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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,380	04/01/2002	Fabrizio Samaritani	P/42-63	7114

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EXAMINER

DEBERRY, REGINA M

ART UNIT

PAPER NUMBER

1647

DATE MAILED: 01/13/2004

✓
SS
Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,380	SAMARITANI ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: |

Status of Application, Amendments and/or Claims

The amendment filed 10 October 2003 has been entered in full. New claims 10-15 were added. Claims 1-15 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-3, 6-10, 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fabbri *et al.*, US Patent No. 5,017,557 in view of Samaritani, WO 95/35116. The basis for this rejection is set forth at pages 2-4 of the last Office Action (13 March 2003).

Applicants state that the Samaritani reference is specifically and explicitly, limited to human growth hormone which consists of 191 amino acids, has a molecular weight of 22,000 and is a linear polypeptide containing two interchange disulfide bridges. Applicants maintain that GRF is a small peptide existing in 44, 40 or 37 amino acids forms with the activity mainly residing in the first 29 amino acid residues.

Applicants state that GRF is very different from HGH and that there is nothing in the Samaritani reference which teaches or suggests that saccharose can be used to stabilize anything other than HGH, much less a peptide which is so very different from the complex large HGH. Applicants state that even if the last sentence in the paragraph of the Samaritani reference could be read to refer to highly purified proteins in general, and in context it is not appropriate to do so, an indication that highly purified proteins

require stabilization does not constitute a suggestion that any and all highly purified proteins can be stabilized by any and all compounds. Applicants assert that there is no basis in such a statement for an expected success and at the very best, the sentence would constitute a suggestion that it would be obvious to try using other stabilizers and obvious to try is insufficient under 103. Applicants conclude by stating that there is no suggestion in the references that GRF can be stabilized by saccharose. The discovery as shown in the examples of the present application and particularly Tables 1-3, that saccharose can be used to obtain a more stable formulation with respect to a formulation stabilized by mannitol, a stabilizer used commercially for GRF, not only lacks predictability, but is surprising and unexpected.

Applicants' arguments have been fully considered but not deemed persuasive for the following reasons. Saccharose, like mannitol is a known protein stabilizer in the art. The specification does not teach that saccharose would specifically denature or destabilize GRF, nor were references cited to demonstrate this. Therefore, there is no evidence that GRF would be expected to behave differently in saccharose. Furthermore, the specification does not demonstrate that the stability results were greater than those that would have been expected from the prior art to an unobvious extent. As was stated above, saccharose is known in the art as a stabilizer/preservative in pharmaceutical formulations. The claimed invention does not have significance equal to or greater than the expected properties. There are no unexpected beneficial results or properties because saccharose is known in the art as a preservative. Thus the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claims 1, 4, 5, 11 and 12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Fabbri *et al.*, US Patent No. 5,017,557 in view of Samaritani, WO 95/35116 and Fujioka *et al.*, US Patent No. 4,963,529. The basis for this rejection is set forth at page 4 of the last Office Action (13 March 2003).

Applicants state that the combination of Fabbri and Samaritani has been discussed and maintain that Fujioki has been cited only to teach lyophilization of a composition containing 10 mg/vial of GRF. Applicants maintain that the Fujioki reference does not cure the basic deficiencies in the prior combination of references.

Applicants' arguments have been fully considered but not deemed persuasive. The Examiner has discussed the combination of Fabbri and Samaritani. Contrary to Applicants' assertion, the Fujioki reference cures the basic deficiency in the prior combination of references. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves *or in the knowledge generally available to one of ordinary skill in the art.* See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claims 1, 2, 13, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fabbri *et al.*, US Patent No. 5,017,557 in view of Samaritani, WO 95/35116 and Tarantino, US Patent No. 5,863,549.

Fabbri *et al.* teach that GRF can be administered by the intravenous route (column 2, lines 47-52). In the clinical trial reported, GRF-29 was used in the form of lyophilized ampoules containing mannitol as an excipient (claims 1, 2). The lyophilized substance was dissolved in 2 ml of physiologic saline. Fabbri *et al.* do not teach the use of saccharose in pharmaceutical compositions or pharmaceutical compositions buffered to a pH between 4 to 6.

Samaritani teaches pharmaceutical compositions comprising human growth hormone (HGH) and saccharose (page 1, lines 1-8). Samaritani teaches pharmaceutical compositions comprising HGH and saccharose, alone or in combination with other stabilizing agents (page 4, lines 17-21)(claims 1, 2).

Tarantino teaches pharmaceutical compositions comprising GRF (column 2, lines 20-29). Tarantino teaches compositions comprising GRF buffered to a pH of 4.0 (column 6, lines 37-44)(claims 13-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Fabbri *et al.*, Samaritani and Tarantino to make the instant invention of a pharmaceutical composition comprising GRF and saccharose buffered to a pH of 6. The motivation and expected success is provided by Samaritani who demonstrates that highly purified proteins can be stabilized with saccharose.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on 9:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



RMD
January 6, 2004



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